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January 22, 2010
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David V. Parker

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Moritz Bünemann *et al.*

Serial No.: 10/538,985

Filed: August 18, 2006

For: MILLISECOND ACTIVATION SWITCH FOR SEVEN-TRANSMEMBRANE PROTEINS

Group Art Unit: 1646

Examiner: Pak, Michael D.

Atty. Dkt. No.: VOSS:008US

Confirmation No.: 2063

DECLARATION OF CARSTEN HOFFMANN

I, Carsten Hoffman, hereby declare as follows:

1. I am a joint inventor of the subject matter disclosed and claimed in the referenced application. I have substantial expertise in the field of seven-transmembrane receptors and, in particular, G-protein-coupled receptors, as evidenced by my enclosed *curriculum vitae*. I am providing this declaration in order to present facts, demonstrating that the subject matter of the invention is fully enabled by the specification.

2. I understand that the subject matter of the invention is currently directed to G-protein coupled receptors comprising at least two detectable labels, wherein such labels are optionally positioned at or on the C-terminus, on the first intracellular loops or on the third intracellular loop. I further understand that the examiner has questioned the enablement of the application, particularly with respect to labels positioned in the first intracellular loop.

3. I understand that the examiner has stated that the specification fails to provide evidence supporting a broad enablement of the present invention. I strenuously disagree. For example, the present application convincingly demonstrates that prominent members of 7-transmembrane receptors, "namely the α_{2A}–adrenergic (neurotransmitter) receptor, the (adenosine) A2A-receptor and the parathyroid hormone (PTH hormone) receptors" (see, *e.g.*, page 7, bottom, of the specification), can indeed successfully be employed in accordance with the present invention (*e.g.* in the context of a "reliable, fast an easy measurement of the activation of such 7-transmembrane proteins"; see page 6 and 7 bridging paragraph, of the specification). This makes it clear that the present application provides evidence that 7-transmembrane receptors can generally be employed successfully in accordance with the teaching of the present application. Further evidence of enablement can be found in the fact that we have shown that a FRET-fluorophore does not negatively affect the receptor function, even if it is inserted into the first intracellular loop (see, *e.g.*, Fig. J, attached hereto). Thus, there is no basis for questioning that the introduction of FRET-fluorophores into other 7-transmembrane receptors will negatively effect their function, i.e. their function of being able to respond as a FRET sensor in a FRET assay according to the teaching of the invention.

4. Further with respect to Figure J, this figure shows the effects of an agonist on the FRET-response of the alpha2A receptor. Relative fluorescence intensity ratio was calculated from fluorescence emission measured at 480nm and at 530nm from cells expressing the receptor sensor and super-fused for the indicated period of time with the agonist nor-epinephrine (NE). The alpha2A receptor was labelled with CFP (donor fluorophore) at the C-terminus and FlAsH (acceptor fluorophore) within the first intracellular loop.

5. Figure J shows that receptor constructs can actually be generated also with labels inserted within the first intracellular loop, proving that functional receptor constructs in accordance with the entire breadth of claim 1 can be achieved. This is irrespective of the biological downstream function of the receptor, for example with respect to G-protein-coupling. Functional G-protein-coupling is not necessary to allow the receptor constructs to respond according to the invention in a receptor FRET assay. Therefore the Examiner's argument against loop 1 or loop 3 constructs at the end of page 5 turn to 6 disturbing G-protein-coupling is plainly invalid. We have shown in several publications (for example Vilardaga *et al.*, *Nature Biotechnology* 2003, Hoffmann *et al.*, *Nature Methods* 2005; both enclosed) that receptors with altered G-protein-coupling do still respond as FRET-sensors in accordance with the teaching of the present invention.

6. In order to further support the above line of argument that the examples provided in the present application can be generalized to basically all G-protein-coupled 7-transmembrane receptors, we herewith provide examples of further G-protein-coupled receptors which have successfully been used in accordance with the present invention. These further examples of G protein coupled receptors are (Figures attached):

(a) the human M1-muscarinic receptor (Figure A and B),

(b) the human M3-muscarinic receptor (Figure C and D),

(c) the human M5-muscarinic receptor (Figure E) and

(d) the human H1-histamine receptor (Figure G and H).

7. Each of the foregoing were labelled at the third intracellular loop and the C-terminus with the combination of FlAsH and CFP. Figures A, C, E and G display the ratio between the CFP and FlAsH fluorescence, whereas Figures B, D and H display the CFP and

FlAsH traces separately. Figure F displays the concentration-effect relationship for the M1, 3 and 5 muscarinic receptors which further underscores the utility of the recombinant G protein coupled receptor constructs of the present invention. All of the above exemplified further 7-transmembrane receptors have already been mentioned in the application as originally filed (see, e.g., page 40 of the specification, middle of the page) and belong to the group of G-protein-coupled receptors.

8. I submit that the foregoing provides strong evidence that the teaching of the present invention is broadly applicable to G protein coupled receptors in general. Furthermore, it is evident that Figure J provides supporting data that also the first intracellular loop can be labelled in order to create functional G protein coupled receptor constructs in accordance with the present invention.

9. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code.

___//January 22, 2010 //_____ _____//Dr. Carsten Hoffmann//_____

Date Carsten Hoffman

Research experience

Group leader

INSITUTE of PHARMACOLOGY & TOXICOLOGY,
UNIVERSITY of WUERZBURG – GERMANY (Prof. M. J. Lohse) **2005 – date**

Research Fellow

INSITUTE of PHARMACOLOGY & TOXICOLOGY,
UNIVERSITY of WUERZBURG – GERMANY (Prof. M. J. Lohse) **2000 – 2004**

Postdoctorial Fellow

NATIONAL INSTITUTES of HEALTH, NIDDK, LBC
MOLECULAR RECOGNITION SECTION – BETHESDA, MARYLAND, USA
(Dr. K. A. Jacobson) **1997 – 2000**

Postgraduate

INSTITUTE of BIOORGANIC CHEMISTRY,
UNIVERSITY of BREMEN – GERMANY (Prof. B. Jastorff) **1993 – 1996**

Training

- Group leader at the Department of Pharmacology – University of Wuerzburg since 2005
- Research Fellow at the Department of Pharmacology– University of Wuerzburg 2000 - 2004
- Visiting Scientist with R.Y. Tsien and M.H. Ellisman– University of San Diego 2003
- Postdoctoral Fellow with K.A. Jacobson – NIH, Bethesda 1997 – 2000
- Visiting Scientist with H. Zimmermann – University of Frankfurt 1998
- Visiting Scientist with M. Veron – Institute Pasteur, Paris 1996
- Visiting Scientist with M. Lanotte – Hôpital St.Louis, Paris 1995
- Visiting Scientist with M. Veron – Institute Pasteur, Paris 1995
- Visiting Scientist with M. Lanotte – Hôpital St.Louis, Paris 1994
- Visiting Scientist with M. Lanotte – Hôpital St.Louis, Paris 1993
- Visiting Scientist with W. Makarewicz – Medical School Gdansk, Poland 1993

Professional

- Member of the German Chemical Society (GDCh) since 1993
- Member of the interest-group Chemical Biology of the (GDCh) since 2005
- Member of the German Pharmacological Society (DGPT) since 2008

Reviewer for Scientific Journals

- British Journal of Pharmacology since 2008
- ACS Chemical Biology since 2008
- Journal of Neurochemistry since 2009

Category A: Original Papers

1. S. Ruchaud, M. Zorn, E. Davilar-Villar, **H.-G. Genieser, C. Hoffmann**, B.T. Gjertsen, S.O. Doeskeland, B. Jastorff & M. Lanotte (1995)
Evidence for several pathways of biological response to hydrolysable cAMP-analogues using a model system of apoptosis in IPC-81 leukemia cells. *Cellular Pharmacology*, 2: 127-140

2. A.C. Skladanowski, **C. Hoffmann**, J. Krass, B. Jastorff & W. Makarewicz (1996)
Structure-Activity-Relationship of cytoplasmic 5`-Nucleotidase substrate sites. *Biochemical Journal*, 314: 1001-1007

3. **C. Hoffmann**, H.-G. Genieser, M. Veron & B. Jastorff (1996)
Novel Synthesis of Nucleoside 5`-Polyphosphates. *Bioorganic & Medicinal Chemistry Letters*, 6: 2571-2574

4. **C. Hoffmann**, S. Raffel, S. Ruchaud, J. Kruppa, M. Zorn, S.O. Doeskeland, M. Lanotte & B. Jastorff(1996)
Chloro-substituted cAMP analogues and their adenosine metabolites induce apoptosis of the human promyelocytic leukemia cell line NB4: molecular basis for celltype selectivity. *Cellular Pharmacology*, 3: 417-428

5. K.-S. Park, **C. Hoffmann**, H.O. Kim, W.L. Padgett, J.W. Daly, R. Brambilla, C. Motta, M.P. Abbrachio & K.A. Jacobson (1998)
Activation and Desenzitation of Rat A3-Adenosine Receptors by selective Adenosine Derivatives and Xanthine-7-ribosides. *Drug Development Research*, 44: 97-105

6. **C. Hoffmann**, S. Moro, R. A. Nicholas, T. K. Harden & K. A. Jacobson (1999)
The role of amino acids in extracellular loops of the human $P2Y_1$ receptor in surface expression and activation process. *J Biol Chem*, 274: 14639-14647

7. S. Moro, **C. Hoffmann** & K. A. Jacobson (1999)
Role of the extracellular loops of G protein-coupled receptors in ligand recognition: A molecular modelling study of the human $P2Y_1$ receptor. *Biochemistry*, 38, 3498-3507

8. M. Kozlowska, R.T. Smolenski, W. Makarewicz, **C. Hoffmann**, B. Jastorff & J. Swierczynski (1999)
ATP depletion, purine riboside triphosphate accumulation and rat thymocyte death induced by purine riboside: a key role of adenosine kinase. *Toxicology letters*, 104: 171-181

9. **C. Hoffmann**, P. Heine, G. Pradel, Y.-C. Kim, K. A. Jacobson & H. Zimmermann (2000)
Inhibition of ecto-Apyase and ecto-ATPrase by pyridoxalphosphate-related compounds. *Drug Development Research*, 51: 153-158

10. K.A. Jacobson, S. Moro, **C. Hoffmann**, Y.-C. Kim, H.S. Kim, R.G. Ravi, T.K. Harden & J.L. Boyer (2001)
Structurally related nucleotides as selective agonists and antagonists at $P2Y_1$ receptors. *Il Farmaco*, 56: 71-75

11. S.G. Kim, G. Ravi, **C. Hoffmann**, Y.-J Jung, M. Kim, A. Chen & K.A. Jacobson (2002)
p53-Independent induction of Fas and Apoptosis in Leukemic cells by an adenosine derivative, Cl-IB-MECA. *Biochemical Pharmacology*, 63: 871-880

12. **C. Hoffmann**, M.R. Leitz, S. Oberdorf-Maass, M.J. Lohse & K.-N. Klotz (2004)
Comparative pharmacology of human β-Adrenergic receptor subtypes – characterization of stably transfected receptors in CHO-cells. *Naunyn-Schmiedebergs Archieves of Pharmacology*, 369:, 151-159

Category A: Original Papers (continued)

13. **C. Hoffmann**, K. Soltysiak, P. West, & K.A. Jacobson (2004)
Shift in purine/pyrimidine base recognition upon exchanging extracellular domains in $P2Y_{1/6}$ chimeric receptors. *Biochemical Pharmacology*, 68: 2075-2086

14. **C. Hoffmann**, G. Gaietta, M. Bünemann, S.R. Adams, S. Oberdorf-Maass, B. Behr, J.-P. Vilardaga, R.Y. Tsien, M.H. Ellisman, M.J. Lohse (2005)
A Flash-based FRET approach to determine G-protein coupled receptor activation in living cells. *Nature Methods*, 2: 171-176

15. P. Hein, M. Frank, **C. Hoffmann**, M.J. Lohse, M. Bünemann (2005)
Dynamics of receptor / G protein coupling in living cells. *EMBO J*, 24: 4106-4114

16. C. Dallanoce, G. Meroni, M. De Amici, **C. Hoffmann**, K.-N. Klotz, C. De Micheli (2006)
Synthesis of enantiopure Δ^2-isoxazoline derivatives and evaluation of their affinity and efficacy profile at human β-Adrenergic receptor subtypes. *Bioorg Med Chem*, 14: 4393-4401

17. B. Behr, **C. Hoffmann***, G. Ottolina, K.-N. Klotz (2006)
Novel mutants of the human β_1-Adrenergic receptor reveals amino acids relevant for receptor activation. *J Biol Chem*, 281: 18120-18125
*Contributed equally

18. V.O. Nikolaev, **C. Hoffmann***, M. Bünemann, M.J. Lohse, J.-P. Vilardaga (2006)
Molecular basis of partial agonism at the neurotransmitter α_{2A}-adrenergic receptor and G_i-protein heterotrimer. *J Biol Chem*, 281: 24506-24511
*Contributed equally

19. P. Hein, F. Rochais. **C. Hoffmann**, S. Dorsch, V.O. Nikolaev, S. Engelhardt, C.H. Berlot, M.J. Lohse, M. Bünemann (2006)
Gs activation is time-limiting in initiating receptor-mediated signalling. *J Biol Chem*, 281: 33345-33351

20. Y. Selz, I. Braasch, **C. Hoffmann**, C. Schmidt, C. Schultheis, M. Schartel, J.-N. Volff (2007)
Evolution of melanocortin receptors in teleost fish: the melanocortin type 1 receptor. *Gene*, 401: 114-122

21. C.A. Jost, G. Reither, **C. Hoffmann**, C. Schultz (2008)
Contribution of fluorophores to protein kinase C FRET probe performance. *ChemBioChem*, 9: 1379-1384

22. **C. Hoffmann**, N. Ziegler, S. Reiner, C. Krasel, M.J. Lohse (2008)
Agonist-selective, receptor-specific interaction of human P2Y receptors with β-arrestin-1 and -2. *J Biol Chem*, 283: 30933-30941
Corresponding author

23. A. Zürn, U. Zabel, J.-P. Vilardaga, H. Schindelin, M.J. Lohse, **C. Hoffmann** (2009)
FRET-analysis of α_{2A}-adrenergic receptor activation reveals distinct Agonist-specific conformational changes. *MolPharm*, 75: 534-541

24. S.Reiner, N. Ziegler, C. Leon, K. Lorenz, K. von Hayn, C. Gachet, M.J. Lohse **C. Hoffmann** (2009)
β-arrestin-2 Interaction and Internalization of the Human P2Y1 Receptor are Dependent on C-Terminal Phosphorylation Sites *MolPharm*, 76: 1162-1171
Corresponding author

Category B: Reviews

1. K. A. Jacobson, **C. Hoffmann**, F. Cattabeni & M. P. Abbracchio (1999)
   Adenosine-Induced Cell Death: Evidence for Receptor Mediated Signalling. *Apoptosis*, 4: 197-211

2. K. A. Jacobson, **C. Hoffmann**, Y.-C. Kim, E. Camaioni, E. Nandanan, S. Y. Jang, D.-P. Guo, X.-d. Ji, I. von Kügelgen, S. Moro, A. U. Ziganshin, A. Rychkov, B. F. King, S. Brown, S. S. Wildman, G. Burnstock, J. L. Boyer, A. Mohanram & K. T. Harden (1999)
   Molecular Recognition in P2 Receptors: Ligand Development Aided by Molecular Modeling and Mutagenesis *Prog. in Brain Research*, 120: 119-132

3. M.J. Lohse, **C. Hoffmann**, V.O. Nikolaev, J.-P. Vilardaga, M. Bünemann (2007)
   Kinetik analysis of G-protein-coupled receptor signaling using fluorescence resonance energy transfer in living cells. *Adv Protein Chem.*, 74: 167-186

4. M.J. Lohse, M. Bünemann, **C. Hoffmann**, J.-P. Vilardaga, V.O. Nikolaev (2007)
   Monitoring receptor signaling by intracellular FRET. *Current Opinion in Pharmacology*,7: 547-553

5. M.J. Lohse, P. Hein, **C. Hoffmann**, V.O. Nikolaev, J.-P. Vilardaga, M. Bünemann (2008)
   Kinetics of G-protein-coupled receptor signals in intact cells. *Br J Pharmacol*,153: S125-S132

6. **C. Hoffmann**, A. Zürn, M. Bünemann, M.J. Lohse (2008)
   Conformational Changes in G-protein coupled receptors – the quest for functionally selective conformations is open. *Br J Pharmacol*, 153: S358-S366
   corresponding author

7. M.J. Lohse, V.O. Nikolaev, P. Hein, **C. Hoffmann**, J.-P. Vilardaga, M. Bünemann (2008)
   Optical techniques to analyze real-time activation and signalling of G-protein-coupled receptors. *Trends Pharmacol. Sci.*, 29: 159-165

8. J.-P. Vilardaga, M. Bünemann, T.N. Feinstein, N. Lambert, V.O. Nikolaev, S. Engelhardt, M.J. Lohse, **C. Hoffmann**
   Minireview: GPCR and G-Proteins: drug efficacy and activation in live cells
   Mol Endocrinol., 2009, 23: 590-599

Category C: Book chapter

1. B. Jastorff, S. Ruchaud, M. Zorn, **C. Hoffmann**, B.T. Gjertsen, S.O. Doeskeland & M. Lanotte (1995)
   Diverse Mechanisms of Induction of Apoptosis through cyclic AMP Analogues: A Possible Target for Drug Design?
   In: Wlodzimierz Mozolowski (1895-1975). W 100-Lecie Urodzin (Ed. W. Makarewicz), Polskie Towarzystwo Biochemiczne, Gdansk, p399-408

2. A.C. Skladanowski, **C. Hoffmann**, J. Krass, W. Makarewicz & B. Jastorff (1994)
   Diffferent substrate specificity of two isozymes of cytosolic 5`-Nucleotidase from rabbit heart. *Adv. Exp. Med. Biol.*, 370: 617-621

3. M.J. Lohse, **C. Hoffmann**, S. Engelhardt (2003)
   Inverse agonism at β1-adrenergic receptors. *International Congress Series,* 2365: 55-61

4. **C. Hoffmann**, M.J. Lohse (2006)
   Fluoreszenzmarkierung von Proteinen in lebenden Zellen: FlAsH-Methode. BIO*spekturm*, 12: 495-497

5. C. Krasel, **C. Hoffmann** (2009)
   Using Intramolecular Fluorescence Resonancs Energy Transfer to study receptor conformation; Chapter 7
   G-Protein Coupled Receptors: Essential Methods, von David Poyner and Mark Wheatley, Wiley-Blackwell

Category C: Meeting Abstracts (of current work)

1. P. Hein, **C. Hoffmann,** M.J. Lohse, M. Bünemann (2007)
   Differential signal amplification in Gs and Gi coupled pathways. *Naunyn-Schmiedebergs Archives of Pharmacology*, 375: 21 Suppl. 1

2. F. Rochais, A. Ahles, **C. Hoffmann,** M.J. Lohse, S.Engelhardt (2007)
   Determination of β1- and β2-adrenergic receptor conformational changes in living cells in real time. *Naunyn-Schmiedebergs Archives of Pharmacology*, 375: 26 Suppl. 1

3. P. Hein, **C. Hoffmann,** M.J. Lohse, M. Bünemann (2007)
   Direct measurement of receptor/Gq-interaction. *FASEB Journal*, 21: A429

4. M. Maier-Peuschel, V.O. Nikolaev, **C. Hoffmann,** M.J. Lohse (2008)
   A FRET-based M2 muscarinic receptor sensor to study the mechanisms of allosteric modulation. *Naunyn-Schmiedebergs Archives of Pharmacology*, 377: 25 Suppl. 1

5. **C. Hoffmann,** P. Hein, U. Zabel, N. Ziegler, C.H. Berlot, M.J. Lohse and M. Bünemann (2008)
   Gq-coupled receptor signaling – A kinetic analysis in living cells. Experimental Biology 2008, programm number 722.1, SanDiego CA, USA April 2008

6. A. Zürn, J.C.Klenk, U.Zabel, M.J.Lohse and **C.Hoffmann** (2008)
   Site-specific two color labelling of proteins with FlAsH and ReAsH in living cells. *EMBL conference on Chemical Biology 2008*, 8-11. October 2008, Heidelberg Germany

7. S. Reiner, M.J.Lohse and **C.Hoffmann** (2009)
   Receptor fingerprinting of the endogenous β2-adrenergic receptor agonists epinephrine and nor-epinephrine. *Naunyn-Schmiedebergs Archives of Pharmacology*, 379: 36 Suppl. 1

Category C: Lectures and Invited seminars

1. The functional role of amino acids within the extracellular loops of the human $P2Y_1$ receptor in surface expression and ligand recognition (Lecture at the Biocenter of the University of Frankfurt, 1998).

2. Role of the extracellular loops of G protein-coupled receptors in receptor activation: a $P2Y_1$ receptor case study (Lecture at the Department of Pharmacology, University of Würzburg, 1998).

3. Development of a fluorescence based test-system to investigate the mechanisms of activation of G protein-coupled receptors: A progress report (Seminar at the NIDDK, National Institutes of Health, Bethesda, 2003)

4. Fluorescence detection of conformational changes upon activation of G protein-coupled receptors (Lecture at the Department of Pharmacology, University of San Diego, La Jolla, 2003)

5. Monitoring G protein-coupled receptor activation in living cells: A Flash-based FRET approach (Invited seminar at the Department of Biochemistry, University of Montreal, 2004)

6. A Flash-based FRET approach to determine G protein- coupled receptor activation in living cells (Blue Seminar Series, EMBL Heidelberg, 2004)

7. Observing G protein-coupled receptor activation in living cells: A Flash-based FRET approach (Invited seminar at the Amsterdam Medical Center, University of Amsterdam, 2005)

8. Novel approaches in Fluorescence detection of conformational changes during GPCR activation (Invited Lecture at the School of Pharmacy, University of Reading, 2005)

9. Observing conformational changes in G protein-coupled receptors: A Flash-based FRET approach in living cells (Invited seminar at the MRC laboratory of Molecular Biology, Cambridge 2005)

10. Observing GPCR activation by novel fluorescence approaches: The tetracystein-tag technology (Invited seminar at the Czech Academy of Science, Prague 2005)

11. Differential Interaction Pattern of the human P2Y Receptors with β-arrestin-1 and -2. (Invited seminar INSERM 301, Strassbourg, June 2006)

12. Site-pecific fluorescent labelling of GPCR's in living cells – shading light on GPCR activation. (Invited seminar Max-Planck-Institute for biophysical chemistry, Göttingen, January 2007)

13. The tetracysteine tag technology – novel approaches to monitor conformational changes of GPCRs in living cells (Invited seminar Boehringer Ingelheim, Biberach a.d.Riss, August 2007)

14. The tetracysteine tag technology: Observing GPCR activation by novel fluorescence approaches (Invited seminar at the GRK760 - University of Regensburg, Regensburg, November 2007)

15. Untersuchungen zur Aktivierung von GPCRs in lebenden Zellen mit Hilfe von FRET (Invited seminar Universität Bonn, Bonn, Januar 2009)

16. Using intra-molecular FRET to study receptor conformations (Invited seminar Universität Graz, Graz, Österreich, Februar 2009)

17. Untersuchungen zur GPCR-Pharmakologie in Echtzeit (Invited seminar BayerHealthCare, Wuppertal, April 2009)

18. A novel FRET technology to study G protein-coupled receptor activation directly in living cells (Invited seminar Addex Pharmaceuticals, Genf, Schweiz Juli 2009)

19. Individual interaction patterns of human P2Y-Receptors with β-arrestin-1 und -2 (Invited seminar Universitätsklinik Düsseldorf, Düsseldorf Juli 2009)

20. Receptor activation studied by site-specific fluorescent labeling of GPCR's in living cells (Invited Lecture University of Nottingham, Nottingham, UK, December 2009)

Category C: Lectures at national and international meetings

1. Identification of Uracil recognition domains in the rat $P2Y_6$ receptor: A $P2Y_{1/6}$ chimeric receptor approach. (42nd spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2001)

2. Comparative pharmacology of human β-receptor-subtypes – characterization of stably transfected receptors in CHO-cells. (43rd spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2002)

3. Distinct receptor selectivity and activity of β-adrenergic receptor ligands. (44th spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2003)

4. A Flash-based FRET approach to determine G-protein coupled receptor activation in living cells. (45th spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2004)

5. Interactions of the human $P2Y_1$ receptor with arrestin-2 and -3. (46th spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2005)

6. A Flash-based FRET approach to determine G protein-coupled receptor activation in living cells. (Short talk at the Gordon Research Conference 'Molecular Pharmacology', Barga, Italy, May 2005)

7. Novel Fluorescence approaches in GPCR activation: the tetracystein tag technology (GPCR day, Weesp, Netherlands, November 2005)

8. Differential Interaction Pattern of the human P2Y Receptors with β-arrestin-1 and -2. (47th spring meeting of the German Society of Pharmacology and Toxicology, Mainz, April 2006)

9. Human P2Y receptors exhibit individual interaction patterns with β-arrestin-1 and -2. (8th International Symposium on Adenosine and Adenine Nucleotides, Ferrara, Italy, May 2006)

10. The tetracysteine-Tag Technology: Applications to GPCR´s and beyond (International Summerschool on molecular Imaging, Heidelberg, Germany, September 2006)

11. Kinetic analysis of the Gq-coupled receptor signalling in living cells (48th spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2007)

12. Visualisation of differential conformational changes within the 3rd intracellular loop of the α2A-adrenergic receptor for full and partial agonists by optical recording in living cells
(Family Resemblance? Ligand binding and activation of family A and B G-Protein-coupled receptors; Biochemical Society focused meeting, GlaxoSmithKline, Stevenage, UK, April 2007)

13. Invited speaker at the Life Science 2007, Session: Lights, camera.... GPCR (New frontiers in GPCR research) Glasgow, UK, July 2007. Invited by Andrew Irvine,

14. Induction of ligand selective conformations by full and partial agonists at the α_{2A}-adrenergic receptor. A FRET study in living cells (GPCR day, Weesp, Netherlands, November 2007)

15. Induction of ligand-selective conformations by full and partial agonists at the α_{2A}-adrenergic receptor – optical recordings in living cells (28th European Winter Conference on Brain Research, LesArc, France, March 2008)

16. Kinetic analysis of the M3-Ach-Receptor activation in living cells (ASPET colloquium, Recent Advances in Muscarinic Receptor Pharmacology & Therapeutics, San Diego, CA, USA, April 2008)

17. Insights into receptor activation by site-specific fluorescent labeling of GPCR´s in living cells (58. Pharmacological days; 3.-5. September 2008, Prag, Tschechische Republik, September 2008)

18. Agonist specific conformations of the alpha2A-adrenergic receptor third intracellular loop in living cells *EMBL conference on Chemical Biology 2008*, 8-11. October, Heidelberg Germany, October 2008)

19. Detection of ligand selective conformational changes at the human M3Ach receptor in living cells (GPCR day, Weesp, Netherlands, December 2008)

20. Ligand selective conformational changes of the human M3Ach-receptor in living cells
(7th annual congress: G Protein-coupled receptors in Drug Discovery, Barcelona, Spain, March 2009)

Category C: Lectures at national and international meetings (continued)

21. Distinct conformational changes of the human M3-acetylcholine-receptor in living cells (50th spring meeting of the German Society of Pharmacology and Toxicology, Mainz, March 2009)

22. FlAsH technology: A method for site specific fluorescent labelling in living cells - applications to Gprotein coupled receptors (3rd focussed meeting on Cell Signalling, University of Leichester, Leichester UK, April 2009)

23. Investigating Ligand-Specific Conformational Changes in Living Cells (2010 Keystone Symposium on G Protein-Coupled Receptors, Apr 7 - Apr 12, 2010, Beaver Run Resort in Breckenridge, Colorado)